REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 0704-0188

1. REPORT DATE *(DD-MM-YYYY)*
7/31/2015

2. REPORT TYPE
Technical Report

3. DATES COVERED *(From - To)*
8/1/2013 – 7/31/2015

4. TITLE AND SUBTITLE
Foldit Biology

5a. CONTRACT NUMBER
N00014-13-C-0221

5b. GRANT NUMBER
N/A

5c. PROGRAM ELEMENT NUMBER
N/A

6. AUTHOR(S)
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5d. PROJECT NUMBER
N/A

5e. TASK NUMBER
1, 2, 3, 4

5f. WORK UNIT NUMBER
N/A

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)
University of Washington, Office of Sponsored Programs
4333 Brooklyn Ave NE
Seattle WA 98195

8. PERFORMING ORGANIZATION REPORT NUMBER

9. SPONSORING/MONITORING AGENCY NAME(S) AND ADDRESS(ES)
Office of Naval Research
One Liberty Center
875 North Randolph St.
Arlington, VA 22203-1995

10. SPONSOR/MONITOR'S ACRONYM(S)
ONR

11. SPONSORING/MONITORING AGENCY REPORT NUMBER

12. DISTRIBUTION AVAILABILITY STATEMENT
Approved for public release; distribution is unlimited.

13. SUPPLEMENTARY NOTES

14. ABSTRACT

15. SUBJECT TERMS

16. SECURITY CLASSIFICATION OF:

a. REPORT	b. ABSTRACT	c. THIS PAGE	17. LIMITATION OF ABSTRACT	18. NUMBER OF PAGES	19a. NAME OF RESPONSIBLE PERSON
Unclassified	Unclassified	Unclassified	SAR		Zoran Popović

19b. TELEPONE NUMBER ***(Include area code)***
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Foldit Biology (Task 1, 2, 3, 4)
Final Report

Period Covered by the Report
August 1, 2013 – July 31, 2015

Date of Report: July 31, 2015

Project Title: Foldit Biology
Contract Number: N00014-13-C-0221
Total Dollar Value:
Program Manager:

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OBJECTIVES

The goal of the Foldit Biology project was to use the effective platform of Foldit as a primary learning vehicle behind an engaging and innovative biology curriculum for high schools and middle schools with the goal of revolutionizing the way biology curriculum is presented for K12 student worldwide.

APPROACH

To achieve this objective, we:

- Created a specific version of Foldit called **Foldit Biology** that presents authored examples of common biological processes;
- Integrated both Foldit and Foldit Biology into a cutting-edge curriculum and activity management tool for classrooms;
- Authored several specific examples of material that can be used in learning situations and which point the way towards future examples;
- Tested the tool in real-world settings.

WORK COMPLETED

Foldit Biology

The Biology version of Foldit was constructed to take advantage of existing Foldit instructional features, such as the dynamic text bubble system. We also inherit the content distribution system from Foldit. This allowed us to dynamically load new updates to the game as well as new lessons or activities. We also added an in-game tutorial system and a help screen; each Foldit Biology example can have its own in-game multi-page tutorial, with each page consisting of text and an image. Each example's tutorial is teacher-editable. Unlike the tutorials, the help screen works like a quick-reference card for the Foldit Biology user interface controls and does not refer to any particular Foldit Biology example.

Foldit Biology additionally supports display of arbitrary PDB data, hidden and displayed atomic targets, protein state transition animations, and undo.

Integration with Teacher Co-Pilot

Crutially, Foldit Biology has been integrated into our Teacher Co-Pilot curriculum delivery system. The Co-Pilot provides Instructional Support (i.e. Lesson Plans), Student Management, Game Delivery, Real-time feedback, and the ability to adapt/differentiate games for different students. Using the Co-Pilot, teachers will be able to start, stop, and pause students as they interact with various examples in molecular biology. Real-time reporting lets teachers see how each student is doing and provide support to those students that need it. Besides delivering lessons, the Teacher Co-Pilot also collects data on teacher and student use. Ultimately, the goal is for the Teacher Co-Pilot to present a detailed plan of activities for classes, consisting of a sequence of interactive activities for both students (e.g. playing Foldit, or solving interactive test problems with the Foldit interface) and the teacher (directing the classroom game play, monitoring class performance, or conducting other interactive activities). The idea is to collect online patterns-of-use data from both students and the teachers. This data in turn will used to optimize the activities in order to produce an optimal online classroom lesson plan. Analysis of Co-Pilot use can be used to inform researchers how teachers are implementing and following the curriculum and utilizing the interactive elements as learning tools for their students. Analysis of student game play will inform the iterative design of Foldit, and other educational games and activities, so that they provide students/players with optimal learning for each student.

Additionally, we are especially interested in the social dynamics of teachers sharing information with each other, crowd-sourcing lesson plans, and how they may be empowered to work collectively to develop optimal curriculum around common stumbling blocks. Over time teachers will be able to modify and alter the online lesson plans on their own and share them with other teachers.

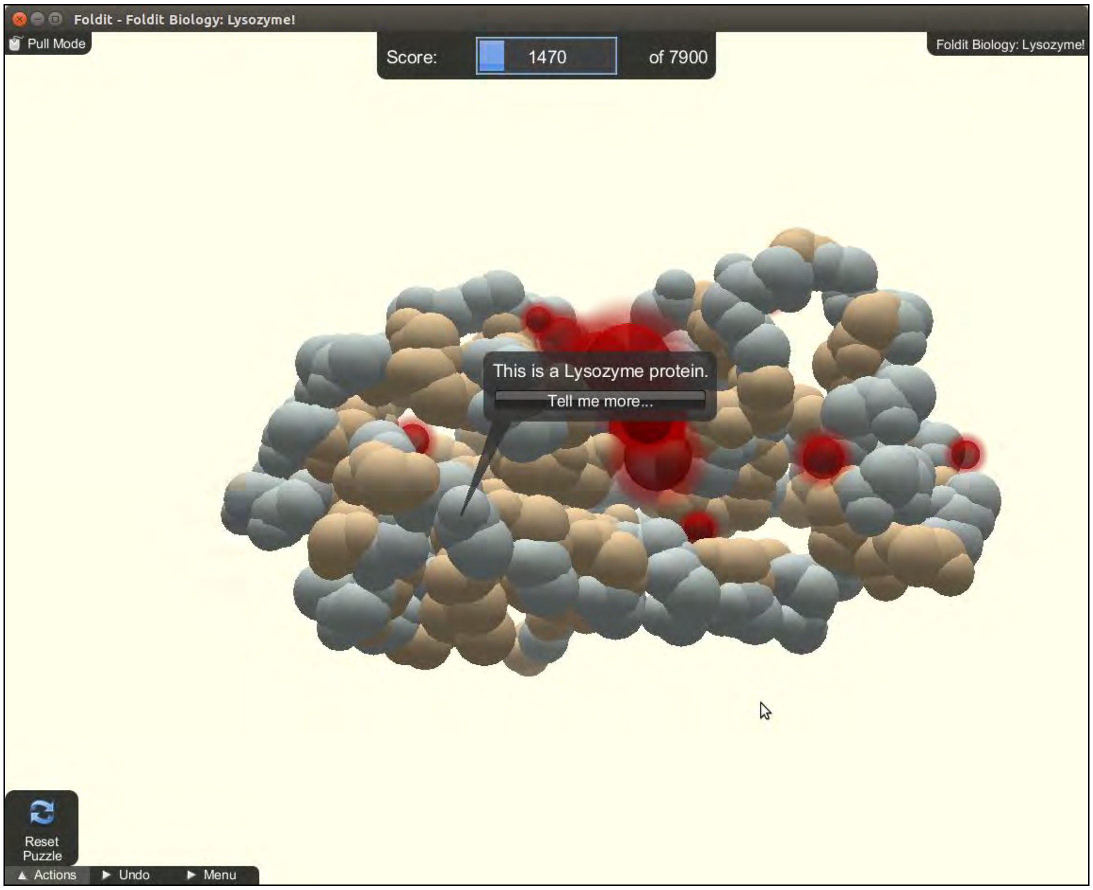
Integrating with the Co-Pilot has also allowed us to simplify much of the interface. Foldit itself no longer has to deal with logging the student in or switching activities/puzzles. The login is handled by the Co-Pilot separately and activity switching is passed as an event from the Co-Pilot. The student only is presented with the activities themselves, so there is no risk of students going off-task or getting stuck within the application.

Curriculum Examples

We have created Foldit-based lessons with several embedded activities that can be used in the classroom. Each student is assigned a computer, and the teacher uses the Teacher Co-Pilot to advance the lesson. When the lesson begins, students start the Foldit Biology Copilot application on their machine. The application displays the message “Eyes up front!” when an activity is not currently underway. When the teacher begins an activity with the “start activity” button, the students’ Foldit clients will start the activities with the corresponding activity IDs. The teacher can pause or resume the current activity. Clicking “Done” for the current activity will put Foldit into pause mode. When another activity is started, the same instance of Foldit will resume and load in the new level. There is Foldit text/photo material for each lesson. We created three main curriculum examples from three common and widely used talking points in the biology curriculum: **Hemoglobin**, **Lysozyme** and **Lactase**.

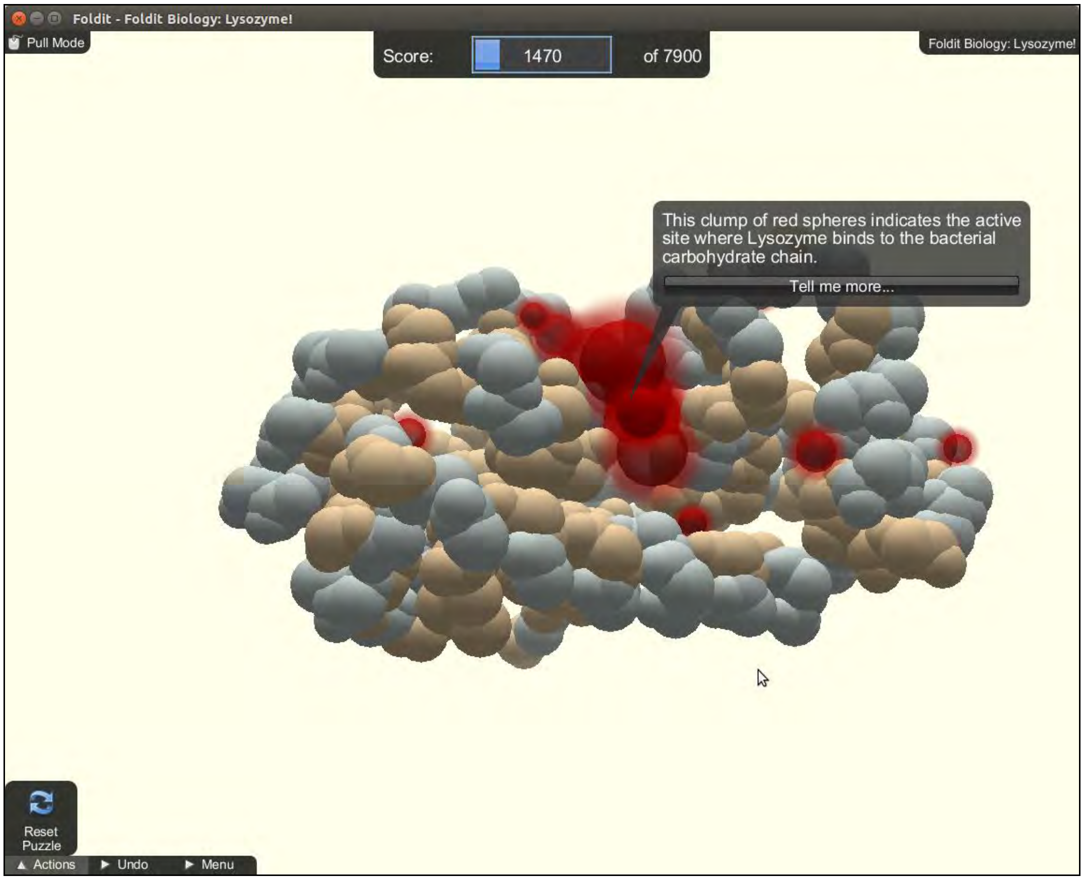
Hemoglobin is our first example and is currently used to show how some of the basic interactive features work in the Foldit Biology prototype, including camera control, navigation, and a subset of visualization options.

The **Lysozyme** example is used to introduce the concepts of how enzymes work, and use a view option to visualize the surface of the enzyme, its active site and its substrate. It is also in this example that we introduce the Foldit Biology notion of a ‘protein state’. Each protein has a unique shape, or conformation, and it is this unique shape that enables the protein to perform its unique function(s) within the organism. Some proteins, such as the enzymes, change from one conformation to another in the course of performing their functions. In Foldit Biology, we say that when a protein’s physical conformation has changed, its state has changed. This is because several things can change when a protein’s shape changes – for example, some of its characteristics, abilities and behaviors can change. Thus the protein’s shape, as well as these other shape-dependent protein quantities, can be gathered together and thought of as a unique state of the protein, or protein state. These states can be named specifically (normal, induced fit, etc.), numbered, or referred to in other ways as necessary.



This is a Lysozyme protein.

Figure 1. Example of the Lysozyme protein activity.



This clump of red spheres indicates the active site where Lysozyme binds to the bacterial carbohydrate chain.

Figure 2. Students are directed through the activity from within the Foldit application, following the text bubbles that direct their attention to the relevant parts of the protein.

Protein states can also be used to associate dynamic quantities of other related molecules with the shape of a protein. For example, we might say that (i) in state #1, the protein is in its normal conformation, and its substrate molecule is far away; (ii) in state #2, the protein is in its induced fit conformation, and its substrate molecule is at the active site; (iii) in state #3, the protein is in its induced fit conformation and its reaction product molecules are at the active site. Note here how states #2 and #3 have the same protein shape, but different quantities of the other molecule. This point illustrates the general usefulness of the protein state abstraction to Foldit Biology, because of its ability to succinctly capture into one package all of the important aspects of a protein interacting with other molecules.

Lactase is the third example, in which we introduce interactive gameplay to show how enzymes work. Like the Lysozyme example, the Lactase example is a multi-state example, consisting of three protein states. In each of the states, in addition to the enzyme, the molecules lactose, sucrose, maltose, galactose, glucose and fructose are present. This example also introduces the Move tool, which can be used to move the various molecules around in the 3D scene. The gameplay challenge for the user is to (i) pick the correct substrate molecule, lactose; (ii) use the Move tool to move the substrate around in the vicinity of the enzyme, searching for the active site; (iii) find the active site and position the substrate at it, triggering the catalysis.

As the molecule that the student is moving gets closer to the active site, the various atoms in the molecule get brighter in color, depending on how close each atom is to its target location in the active site. When all the atoms are fully bright, the molecule has arrived at the active site, and the enzyme will switch state. Thus the atom colors serve as a hinting mechanism to help the student decide where to guide the molecule as he/she is searching for the active site. This feature can also help the student rule out non-substrate molecules, because the atoms of non-substrate molecules will not light up as fully as those of substrate molecules.

After the activity has finished, the teacher can press Done, which will display the “Eyes up front!” message for all Foldit users once again.

RESULTS

Northwest Association for Biomedical Research (NWABR)’s Camp BIOmed summer camp program, which took place July 7-August 15, 2014, was the first deployment of the Foldit Biology curriculum. This was a local program that offered to high school students over multiple weeks over the summer. The test was successful and the information gathered from use in these summer camps was invaluable towards our larger goal of deploying of Foldit Biology at scale to all biology teachers worldwide at the end of the year.

Based on feedback throughout the reporting period, we have implemented a large number of small features and improvements in response to requests and other discussions:

- Any installation of Foldit now Co-Pilot capable
- Foldit will now start when an activity begins, and close when it ends (there is a brief message before closing)
- Improved loading times (Foldit)
- Improved connection reliability (Foldit)
- Refactored the interface code in Co-Pilot for ease of understanding and maintainability.
- Protein position & orientation is locked, so users won’t move it by accident when trying to move the ligand/substrate

- Prominent messages are displayed on-screen when the user has successfully bound or docked a ligand/substrate
- The initial camera view is set to a more user-friendly setting in all built-in examples
- Side chain display and atom coloration now have the better default settings

IMPACT/APPLICATIONS

Since Foldit is a natively compiled C++ application, we developed a generic Flash "wrapper" application that runs in the browser where Co-Pilot integrated games normally run. This wrapper application opens a socket connection to the native executable, allowing it to forward any API calls to and from the native application. On the Foldit side, we have created a C++ class that may be plugged into any C++ application to communicate with the Flash link application. This class runs in its own thread and handles all communication with the Flash application. The integrating application is responsible only for starting up the thread itself, and then registering function calls for each of the available events from the API. This makes the process of integrating a C++ program very similar to the process for standard Flash applications. The end result is that Foldit can be integrated into our Co-Pilot Framework with no changes to the Framework itself. It is worth noting that this approach can now be applied to any native executable; all that is necessary is modification of the native application to allow it to listen on a socket and implement the functionality required by the API calls. This is a great result of the development effort towards Foldit Biology and will continue to prove useful for both Foldit's use in education and for education research at the Center for Game Science generally.

Another exciting development for the future is the fact that the main Foldit project is currently being improved with a number of features intended for drug design. We are planning on posing the community simple drug design puzzles that will then scale to more complex problems. For the first puzzle, we are going to release an HIV protease. This is because HIV protease has a lot of preexisting information associated with it. This will let players test their skills and give us an idea on what type of things they design and if they are related to known small molecule binders. These drug design features will subsequently be accessible to educators using Foldit Biology, and could be used to illustrate a wide variety of situations in which small molecules interact with larger proteins.

PUBLICATIONS

Press:

- NWABR: Camp BIOmed 2014 Report
- SynBioBeta: Can Video Games Inspire the Next Generation of Biohackers?
- New York Times: Not Just Playing Around Anymore